

Histopathological Analysis as Support for the Applicability of Interval Appendectomy: A Single-Center Retrospective Study

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Abstract: *Background:* The management of perforated appendicitis with abscess, including interval appendectomy, remains controversial. *Materials and Methods:* The study was a retrospective analysis of patients diagnosed as having perforated appendicitis with abscess who were treated in our hospital between April 2014 and December 2020. A total of 51 patients who underwent successful interval appendectomy protocol were included. Residual pathological inflammation in the resection specimens and the relationship between preoperative computed tomography imaging and residual inflammation findings were evaluated. *Results:* All patients who had successful interval appendectomy received laparoscopic appendectomy as an elective surgery. Postoperative complications included superficial surgical site infection in two patients (4%). Pathological assessment of the resection specimens of interval appendectomy revealed acute inflammation and chronic inflammation in 11 patients (22%) and 25 patients (49%), respectively. Preoperative computed tomography imaging showed elevated peri-appendiceal fat tissue concentration and residual abscesses in 11 patients (22%) and five patients (10%), respectively. Residual inflammation was significantly higher in patients who had exhibited elevated peri-appendiceal fat tissue concentration on preoperative computed tomography imaging. *Conclusions:* Despite the absence of abdominal pain or other inflammatory symptoms, 70% patients showed pathological evidence of ongoing inflammation even after 3 months of conservative treatment. Given the high percentage of resection specimens showing acute or chronic appendicitis, interval appendectomy should be performed for complete elimination of inflammation.

Keywords: Interval Appendectomy, Computed Tomography, Inflammation, Pathology

1. Introduction

Acute appendicitis is one of the most common surgical diseases with a lifetime occurrence of 12% [1]. Approximately 25% of newly diagnosed cases of acute appendicitis present with complicated appendicitis due to post-perforation [2]. The initial management of stable patients with antibiotics and percutaneous abscess drainage, if applicable, is well accepted. However, the risk of recurrent appendicitis as well as the rationale and timing of interval

appendectomy is still debated.

Successful interval appendectomy treatment in the pediatric field has led to its employment for complicated appendicitis in the adult field. In recent years, an increasing number of reports have shown the usefulness of interval appendectomy in adult patients [3, 4]. We have actively promoted the interval appendectomy protocol for perforated appendicitis with abscess for all ages since its introduction in April 2014. The usefulness of the interval appendectomy protocol, including its low incidence of complications and cost-effectiveness has been reported [5]. The recurrence rate of appendicitis in children

after conservative treatment is 8% to 20% [4, 6]. Although appendicitis recurrence rate after conservative treatment as a basis for interval appendectomy indication is often discussed, there are few reports that examine the necessity of interval appendectomy from a pathological perspective.

The hypothesis of this study is that residual inflammation in resection specimens after conservative treatment will prove the need for interval appendectomy for complete elimination of inflammation. The perioperative results of interval appendectomy for perforated appendicitis with abscess were analyzed and the necessity of interval appendectomy was discussed from a pathological standpoint.

2. Materials and Methods

2.1. Patients

This retrospective, single-center observational study included patients diagnosed as having perforated appendicitis with abscess, for whom the interval appendectomy protocol was indicated at our department between April 2014 and December 2020. The eligibility criteria for the interval appendectomy protocol were as follows: 1) fluid accumulation of 1 cm or more around the appendix suspicious for abscess formation on computed tomography imaging; 2) non-diffuse peritonitis; and 3) presence or absence of coprolite and patient age were not considered. Any of the following conditions were excluded: 1) unstable vital signs; 2) comorbidity that prioritized surgery, such as chronic renal failure or pregnancy; and 3) presence of artificial objects in the body, such as intravascular stents, central venous ports, or pacemakers. Written informed consent was obtained from all the patients who underwent the interval appendectomy protocol. The study protocol was approved by the Institutional Review Board of the Kobe City Medical Center General Hospital. Informed consent for use of the patients' data was waived because of the retrospective study design.

2.2. Procedure of Interval Appendectomy Protocol

Once perforated appendicitis with abscess was diagnosed, intravenous antibiotic (cefmetazole or meropenem) treatment was initiated, with percutaneous drainage in possible cases after initial hospitalization. After resolution of abdominal pain and leukocytosis, the patients were permitted to leave the hospital with a prescription for oral antibiotics for approximately 14 days. Colonoscopy was performed to exclude the possibility of malignancy complications in adult patients with complicated appendicitis. After assessing the condition of the surrounding appendix with computed tomography imaging, interval appendectomy was routinely scheduled for 3 months (2 months in appendicolith cases) following discharge from the initial admission.

2.3. Outcomes

Perioperative data was obtained and reviewed from the patients' medical records. The primary outcome was the incidence of pathological inflammation and its association

with the preoperative computed tomography imaging findings. The secondary outcome was the usefulness of the interval appendectomy protocol, including protocol completion rate, postoperative complications after interval appendectomy, and detection rate of malignant tumors.

2.4. Pathological and Statistical Analyses

Several pathologists evaluated and diagnosed the resection specimens. A single pathologist reviewed and classified the pathology results for each case as acute inflammation, chronic inflammation, or no inflammation. Cases with many neutrophils were classified as having acute inflammation, those with lymphocytes and macrophages as chronic inflammation, and those with fibrotic cells as no inflammation.

Continuous and categorical variables were analyzed using the Student's *t*-test and Fisher's exact test. All statistical analyses were conducted using JMP version 12 (SAS Institute Inc., Cary, NC, USA). A *p*-value of <0.05 was considered statistically significant.

3. Results

Between April 2014 and December 2020, 759 patients with acute appendicitis were treated with appendectomy at our department. Among them, 701 patients with uncomplicated appendicitis underwent emergency surgery, and 58 patients having perforated appendicitis with abscess were indicated for the interval appendectomy protocol. Three patients deviated from the protocol due to the development of abdominal pain during conservative treatment, and 55 patients were successfully treated conservatively. Interval appendectomy was performed in 51 patients, excluding four patients who presented with malignant tumors on colonoscopy. The patient selection process is shown in Figure 1.

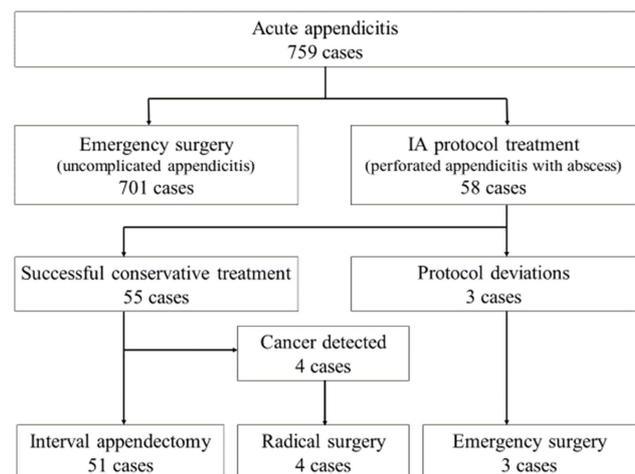


Figure 1. Treatment flow chart.

Emergency surgery is performed for uncomplicated appendicitis, and interval appendectomy protocol is applied for perforated appendicitis with abscess. IA: interval appendectomy.

Patient characteristics of all indicated interval appendectomy

cases are compared with the conservatively treated success cases and failure cases in Table 1. The average patient age was 54 years. The success and failure cases did not show differences in abscess size or degree of inflammation on blood examinations, such as white blood cell count and C-reactive

protein levels. A total of 22 (38%) patients underwent percutaneous drainage during the initial admission. In the three protocol deviation cases with worsening clinical course, the required percutaneous drainage was technically difficult due to overlapping of the intestinal tract or other factors.

Table 1. Patient characteristics.

Variable	All cases	Success cases	Failure cases	P-value
n	58	55	3	
Age (years)	54±20	53±3	47±9	0.406
Sex	Male	29	1	0.467
	Female	28	2	-
Body mass index (kg/m ²)	21.8±3.2	21.9±3.3	21.9±2.4	0.955
White blood cell count (cells/μL)	13630±4570	13720±4530	12570±5750	0.748
C-reactive protein (mg/L)	12.9±6.3	13.0±6.2	11.7±9.4	0.985
Size of abscess (cm)	39.4±16.2	39.7±16.6	34.0±15.5	0.584
Appendicolith	Yes	9	0	0.425
	No	49	3	-
Drainage of abscess	Yes	22	0	0.140
	No	36	3	-

A summary of the perioperative outcomes of the patients for whom interval appendectomy protocol was indicated is given in Table 2. Computed tomography imaging followed up before surgery showed elevated peri-appendiceal fat tissue concentration in 11 patients (22%) and remaining abscess in five patients (10%) despite normalization of inflammation on blood examinations and absence of abdominal pain. The mean time of discharge from the first

admission to interval appendectomy was 101 days. All patients who underwent interval appendectomy were able to receive laparoscopic appendectomy and were not transferred to extended surgery, such as laparotomy or ileocecal resection. Only two patients had postoperative complications of superficial surgical site infection. The mean length of stay was 11 days on initial admission and 3 days on second admission.

Table 2. Perioperative outcomes.

Variable	Success cases	Failure cases
Fat tissue concentration	Elevated	11
	None	40
Abscess	Remained	5
	None	46
Time to appendectomy (days)	101±46	-
Operation method	Laparoscopic appendectomy	51
	Converted to laparotomy	0
Operation time (min)	84±48	125±13
Blood loss (mL)	4±17	17±29
Length of stay, initial admission (days)	11±4	12±1
Length of stay, second admission (days)	3±1	-
Postoperative complications	None	49
	Superficial SSI	2
	Residual abscess	0

Superficial SSI: superficial surgical site infection.

Table 3. Pathological outcomes.

Variable	
Pathological finding	Phlegmonous appendicitis
	Catarrhal appendicitis
	Chronic appendicitis
	Fibrosis or granulation tissue
	Others
Residual inflammation	Acute inflammation
	Chronic inflammation
	None

Pathology reports of all patients following interval appendectomy are listed in Table 3. The pathological findings identified phlegmonous appendicitis in eight cases

(16%), catarrhal appendicitis in three cases (6%), chronic appendicitis in 25 cases (49%), fibrosis or granulation tissue in 12 cases (24%), and mucocele in one case (2%). Further,

pathological appendix without inflammation was detected in 15 cases (29%), residual acute inflammation in 11 cases (22%), and residual chronic inflammation in 25 cases (49%). Patients with elevated peri-appendiceal fat tissue concentration on preoperative computed tomography

imaging showed significantly higher residual pathological inflammation than patients with normal peri-appendiceal fat tissue concentration ($p=0.007$). Residual abscesses on imaging did not correlate with residual pathological inflammation (Table 4).

Table 4. Correlation between preoperative imaging and pathological findings.

Variable		Acute inflammation	Chronic inflammation	None	P-value
Fat tissue concentration	Elevated	5	6	0	0.007
	None	6	20	14	
Abscess	Remained	2	2	1	0.607
	None	9	23	14	

4. Discussion

Conservative management of complicated appendicitis has become the preferred treatment strategy. However, the necessity of elective surgery remains controversial. Most reports on the usefulness of interval appendectomy have been in pediatric surgery and not in adult surgery. Despite the absence of abdominal findings and inflammatory response on blood examination, evidence of ongoing inflammation was observed in 70% of cases on histopathological analysis of the interval appendectomy specimens, which was comparable to previous reports of 60%–91% of remnant inflammation in the adult field [3, 7, 8]. Pathological abnormalities, including remnant inflammation, may predispose patients to recurrent appendicitis. Additionally, the activity of chronic inflammatory cells is associated with neoplastic transformation and stimulation of cancer growth [9]. The relationship between persistent gastritis induced by *Helicobacter pylori* and gastric cancer as well as type B and C hepatitis and hepatocellular carcinoma has already been reported [10, 11]. Approximately 25% of cancers are associated with chronic inflammation [12]. For the complete removal of inflammation in perforated appendicitis with abscess, non-operative management is not curative for at least several months. The study's reported lower postoperative complication rate of 4% is acceptable when compared to that of previous reports; thus, elective appendectomy after conservative treatment is necessary and acceptable [13, 14].

It is difficult to evaluate the presence of residual inflammation when deciding whether to perform an elective appendectomy. However, in this study, there was a correlation between elevated fat tissue concentration on preoperative computed tomography imaging and pathological residual inflammation. Residual small abscesses were sometimes found at sites distant from the appendix, which may be partly due to their lack of association with residual pathological inflammation. Therefore, computed tomography imaging showing elevated residual peri-appendiceal fat tissue concentration with suspicion of residual inflammation indicates interval appendectomy for removing inflammation.

The selection of an appropriate time interval before elective appendectomy is important. A short time interval leads to increased difficulty in surgical procedures due to adhesions, while a long time interval leads to increased recurrence rates.

The time interval for interval appendectomy is generally 10–13 weeks [1, 4, 8]. Patients with fecaliths after initial non-operative treatment of perforated appendicitis had an increased risk of recurrence [15, 16]. Therefore, it is necessary to shorten the time interval for patients with fecaliths. The time interval for elective surgery, which was set at 3 months (2 months in appendicolith cases), was considered appropriate because there were no cases of recurrence during this time interval. Additionally, most cases did not have strong adhesions associated with inflammation, which would make surgical manipulation difficult.

A further disadvantage of not undergoing interval appendectomy is the risk of missed pathological findings. A recent randomized controlled trial, which was terminated early, showed a high rate of neoplasms (17% overall and 24% in patients greater than 40 years old) [17]. In the current study, malignancy was found in 7% of patients treated conservatively for perforated appendicitis with abscess. In the adult field, the possibility of malignancy is observed at a certain rate. To avoid multiple surgeries, including radical resection, screening tests for malignancy, such as colonoscopy after conservative treatment, is as necessary and effective as the interval appendectomy protocol.

Our study has several limitations. This was a single-center retrospective study with a relatively small sample size. The lack of a comparison group that was managed by only conservative treatment with no interval appendectomy limited our ability to effectively assess the treatment strategy. The duration of antibiotic administration, including oral antibiotics, varied depending on the physician's discretion due to the absence of a clear antibiotic treatment period. This difference in the duration of antibiotic administration may have affected residual inflammation, such as remnant abscess and elevated peri-appendiceal fat tissue concentration.

As a future prospect, further accumulation of cases with complicated appendicitis and randomized studies are expected to investigate the usefulness of interval appendectomy. It is also considered necessary to examine the difference in pathological residual inflammation depending on the timing of interval appendectomy, with a clear antibiotic administration period.

5. Conclusions

In this study, 70% of patients who underwent interval

appendectomy showed residual active and chronic inflammation on surgical pathology analysis even after 3 months of initial conservative treatment. Interval appendectomy was safely performed, with few postoperative complications. Given these findings, appendicitis with abscess managed with conservative treatment, especially in patients with elevated peri-appendiceal fat tissue concentration on computed tomography imaging, requires additional treatment including interval appendectomy.

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